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EXAMINER
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ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,350	WU ET AL.	
	Examiner	Art Unit	
	BO PENG	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-74* is/are pending in the application.

4a) Of the above claim(s) *17-22,24-53,61 and 66-70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,23,54-60,62-65 and 71-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 February 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/10/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Restriction election

1. Applicants' elections, without traverse, of Group I, and the following species in the reply filed on July 6, 2009, are acknowledged. Applicants elected the species of a polypeptide sequence 1 of SEQ ID NO: 6, sequence 2 of SEQ ID NO: 23, sequence 3 of SEQ ID NO: 48, the linking peptide of AAA between sequence 1 and 2, and GGG between sequence 2 and 3, and CH3(CH2)14CO- as modifying group (Claims 7-15), an injection formulation in Claim 59, and a lyophilized liposome dosage of Claim 72. The requirement is deemed proper and is therefore made FINAL.

2. Accordingly, Claims 1-74 are pending. Claims 42-53 and 70 have been withdrawn by Applicants. Claims 17-22, 24-41, 61 and 66-69 are withdrawn from further consideration by the Examiner, under 37 C. F. R. 1.142(b), as being directed to a nonelected invention. Claims 1-16, 23, 54-60, 62-65 and 71-74 are examined in this Office action.

Information Disclosure Statement

3. The information disclosure statement submitted on February 10, 2006, is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner. An initialed and dated copy of Applicant's IDS form 1449 is attached to the instant Office action.

Claim Rejections - 35 USC § 112, second paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 2 and 3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 2 and 3 are indefinite because the term "variant sequences thereof" is not explicitly defined in either the claims or the specification. One of ordinary skill in the art cannot be reasonably apprised of the metes and bounds of the invention because it is not clear what function is intended.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

7. Claims 1, 6 and 54-60 are rejected under 35 U.S.C. 102(a) as being anticipated by Madalinski K, *et al.* (Vaccine, 2001, 20(1-2):92-7. Note: Although the paper shows "Vaccine 20 (2002) 92-97" on its front page, it appears to be a print error. As indicated by the *Vaccine* journal, *Vaccine* 20, issues 1-2, 2001, was published on 12 October, 2001, Available online 19 September 2001), as evidenced by Heermann, (*J Virol* 52 (1984), p. 396-493), Tam (PNAS 86:9084-9088, 1989) and Roh (Virus Res. 73:17-26, 2001).

8. Claim Interpretation:

(1) Claims 1, 6 and 54-60 read on a polypeptide **comprising** sequence 1 of T helper epitope, sequence 2 of CTL epitope form hepatitis B virus and sequence 3 of B cell epitope from

hepatitis B virus, wherein the sequence 1-3 are covalently linked together by linking peptides (Claim 1), wherein said sequences 1-3 can be in any order of 1-2-3; 1-3-2; 2-1-3, 2-3-1, 3-1-2 or 3-2-1. Since any amino acids can serve as linker peptides, the claims read on any protein or peptide comprising a T helper epitope from any source, a CTL epitope from hepatitis B virus and a B cell epitope from a hepatitis B virus.

(2) Claims 54 and 55 recite: "..., wherein the vaccine is suitable for treatment of a chronic HBV persistent infection state and relevant secondary diseases selected from the group consisting of liver cirrhosis and liver cancer", "...wherein the chronic HBV persistent infection state occurs in a patient with chronic hepatitis B or a carrier of hepatitis B virus". However, such "wherein" clause is interpreted as intended use, but not a limit to the claimed vaccine. According to MPEP 2111.04 [R3], such "wherein" clause does not limit the scope of the claim because it does not limit the claims to a particular structure.

9. Madalinski K, *et al*. teaches that the large surface proteins of HBV (large HBs) comprising preS1, preS2 and S antigens can be used as human vaccines, See e.g. Abstract, and Para 1, right col. p.93. As evidenced, Heermann, *et al.* teaches the sequence of large HBs. Tam teaches that the large HBs comprises a T epitope in amino acid residues 12-26 of the pre-S2 region, and a B cell epitope in the 140-146 residues of the S region, (see e.g. Abstract, and right col. p.9084). Roh teaches the CTL epitope between amino acids 179-186 of the surface protein (see e.g. Abstract). Since the large HBs surface polypeptide of the prior art meets the structural limitations of Claims 1, 6 and 54-60, the subject matter of the claims is anticipated by Madalinski.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1-16, 23, 54-60, 62, 63 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vitiello (US 6,322,789) and Tam (PNAS 86:9084-9088, 1989).

12. Vitiello teaches following:

(a) a polypeptide immunogen or a vaccine comprising T helper epitopes and HBV CTL epitopes; See e.g. Para 4, col. 2 to col.4; and Para 3, col. 12. Specific T helper peptide from tetanus toxoid SEQ ID NO: 14 is 100% identical to the claimed sequence 1 of SEQ ID NO: 6; and a CTL epitope of SEQ ID NO: 23 is 100% identical to the sequence 2 of SEQ ID NO 23, see sequence alignment below:

```
Qy          1 QYIKANSKFIGITE 14          Vitiello SEQ ID NO: 15
              ||||||||||||||
Db          1 QYIKANSKFIGITE 14          sequence 1 of SEQ ID NO:6


Qy          1 FLPSDFFPSV 10              Vitiello SEQ ID NO: 23
              ||||||||||
Db          1 FLPSDFFPSV 10              sequence 2 of SEQ ID NO:23
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(b) The epitopes are covalently linked together by linking peptides, such as AAA or GGG, see e.g. Para 1 and 2, col. 13.

(c) said polypeptide can be modified with palmitic acid $CH_3(CH_2)_{14}COOH$ at the *N*-, or *C*-termini, or any side chain group of said polypeptide. see e. g Para 1-3, col. 13; Exemplified

polypeptide modified with palmitic acid (PAM) $CH_3(CH_2)_{14}COOH$ at its *N*-terminal, see e.g. Example I and VI.

(e) Vitiello shows the (PAM2KSS-T helper-CTL and (PAM)2 KSS-T helper-AAA-CTL were superior to induce immune responses when injected into mice, see Example IV-VI.

(d) said peptide immunogen or vaccine is administered via liposome comprising phospholipids, palmitic acid, see e.g. Para 3, co. 18, and bridging Par between col. 18 and col. 13. Vitiello does not explicitly teach incorporating SEQ ID NO: 48 in the peptide.

14. Tam teaches a synthetic peptide immunogen or vaccine comprising HBV T and B cell epitopes , wherein the T and B cell epitopes are covalently linked together by linking peptides, see e.g. Abstract, and Fig. 1, wherein the B cell epitope comprises amino acid sequence 100% identical to the claimed sequence 3 of SEQ ID NO: 48, see sequence alignment below.

```
1 LQDPRVRGLYFPAGG 15          Tam
    ||||||||||
1   DPRVRGLYFPA 11           sequence 3 of SEQ ID NO: 48
```

Tam teaches that MAP can enhance immune responses and overcome the poor immunogenicity encountered with a single epitope.

> MPEP § 2144.06 recites the conclusions of In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA), "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose…[T]he idea of combining them flows logically from their having been individually taught in the prior art."
>
> The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

15. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the

invention was made to make a polypeptide comprising T helper, CTL and B cell epitopes in order to enhance immunogenicity of the vaccine. One skilled in the art would have been motivated to generate the claimed invention with a reasonable expectation of success, given that the combination of T-helper and CTL epitopes, as well as B cell epitopes can result in increased immunogenicity as taught and demonstrated by Vitiello and Tam. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. Claims 64, 65, 71 and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vitiello (US6,322,789) and Tam (PNAS 86:9084-9088), as applied to Claims 1-16, 23, 54-60, 62, 63 and 65 above, further in view of Schneider (US 6,333,021)

17. The relevance of Vitiello and Tam are set forth *supra*. However, neither Vitiello nor Tam teaches the liposome formula further comprising cholesterol, vitamin E, mannitol, or human albumin.

18. Schneider provides teachings indicating that those chemical are known integrates for forming liposomes. For example, See example 1 and 7, and the claims for cholesterol, palmitic acid, vitamin E, mannitol, and albumin.

19. Although Schneider does not explicitly teach the ratio of Claim 72, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A. Since all claimed chemicals are well known in the art for their application to making liposomes, they are obvious choices for use as

the adjuvant of the instant vaccine. The specific formula of Claim 72 can be obtained by routine optimization by one of ordinary skill in the art. Therefore, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

20. Claims 73 and 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heathcote (Hepatology. 1999 Aug;30(2):531-536), in view of Tam (PNAS 86:9084-9088, 1989) and Vitiello (US6,322,789).

21. Heathcote teaches a method of inducing immune responses in HBV-infected patients comprising administering a peptide T-helper and CTL epitopes, called as CY-1899, see e.g. Abstract. CY-1899 has a structure of palmitic acid $CH_3(CH_2)_{14}CO$-KSS-QYIKANSKFIGITE-AAA- FLPSDFFPSV, which the structure features 100% identical to those of the claimed vaccine, inducing palmitic acid, and sequence 1 of SEQ ID NO: 6, AAA linking peptide, and sequence 2 of SEQ ID NO: 23. Heathcote teaches that administration of the single-epitope vaccine, CY-1899, initiated CTL activity, but at an order of magnitude lower level than that observed during spontaneous HBV clearance.

22. Heathcote does not teach the vaccine further comprises sequence 3 of SEQ ID NO: 48.

23. The relevance of Tam and Vitiello are set forth *supra*.

24. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Heathcote by including B cell epitope in the vaccine to enhance immune responses in the patients as taught by Tam. One skilled in the art would have been motivated to generate the claimed invention with a reasonable expectation of success given that combination of T-helper and CTL epitope, as well as B cell epitopes can result

in increased immunogenicity as taught and demonstrated by Vitiello and Tam. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Remarks

25. No claims are allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bo Peng, Ph.D. whose telephone number is 571-272-5542. The examiner can normally be reached on Tu-F, 8:30-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/BO PENG/
Primary Examiner, Art Unit 1648